REMARKS

The present invention relates to antibodies that specifically bind to the cardiac-specific troponin I in both free and complexed forms in an immunoassay. In particular, the instantly claimed antibodies insensitve to various forms of cardiac troponin I, including cardiac troponin I in free, binary, and tertiary troponin complexes.

Claims 55-78 are pending in the instant application, with claims 69-74 currently under examination. Applicants have cancelled claims 55-68 and 75-78 herein, and added new claims 79-93 herein. Applicants respectfully submit that the new claims do not introduce new matter or require a new search. The new claims are fully supported by the specification as originally filed, *e.g.*, on page 8, lines 19-25; page 11, lines 18-30, and page 13, lines 26-32.

Notwithstanding the foregoing, Applicants expressly reserve the right to pursue subject matter no longer claimed in the instant application in one or more applications which may claim priority hereto. Applicants respectfully request reconsideration of the claimed invention in view of the foregoing amendments and the following remarks.

Non Art-Related Remarks

Oath/Declaration

The Examiner contends that the present declaration is defective, and requests a new oath or declaration identifying this application by application number and filing date. Paper No. 6, page 3.

It is respectfully submitted that the present application is a continuation of U.S. Application serial No. 08/633,248, filed April 18, 1996, now Patent No. 6,174,686. As such, a copy of the corresponding declaration in compliance with 37 CFR 1.67(a) from the parent file can be used for the current application. That declaration, originally filed in the instant application on October 12, 2000 and enclosed herewith as Appendix C, does provide the names and post office addresses for all inventors. In view of acceptance of this declaration in the parent

application, Applicants respectfully request that the Examiner's clarify the reasons why the declaration is not acceptable in the instant application.

Abstract

The Examiner has objected to the abstract provided in the application as filed. Applicants gratefully acknowledge the Examiner's comments, and provide herewith a new abstract in the proper format.

Priority

Applicants respectfully submit that the specification has been amended herein to reflect the appropriate priority claim.

Information Disclosure Statement:

The Examiner has acknowledged the submission of the Information Disclosure Statement in Paper No. 3. However, some of the references were not considered by the Examiner because the Examiner has asserted that either no copies of these references were provided, or no English translation or a statement of relevance were provided. Applicants note that, with the exception of three German Patents, each item listed in the Information Disclosure Statement was submitted in the parent application, and should, therefore, be considered by the Examiner in the instant application. Applicants resubmit herewith the remaining three German Patents, with a statement of relevance for each (*i.e.*, an English language abstract), in a new Information Disclosure Statement, and respectfully request that each be considered by the Examiner.

35 U.S.C § 112, Second Paragraph

The Examiner has rejected claims 69-74 under 35 U.S.C. § 112, second paragraph, alleging that the claims are indefinite for failing to particularly point out and distinctly claim the present invention. Applicants respectfully traverse this rejection

When determining definiteness, the proper standard to be applied is "whether one skilled in the art would understand the bounds of the claim when read in the light of the specification." *Credle v. Bond*, 30 USPQ2d 1911, 1919 (Fed.Cir.1994). See also *Miles Laboratories, Inc. v. Shandon, Inc.*, 27 USPQ2d 1123, 1127 (Fed.Cir.1993) ("If the claims read in the light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more.").

Antecedent basis

Applicants respectfully disagree with the Examiner's contention that claims 72-74 allegedly lack proper antecedent basis in reciting "A method according to claim 'x.'" The language to which the Examiner objects indicates that the claim refers back to, and further limits, claim x, in accordance with 37 C.F.R. § 1.75. Applicants respectfully submit that MPEP 608.01(n) specifically describes the use of the indefinite article in the context of multiple dependent claims.

Furthermore, although the examples in the MPEP refer to multiple dependent claims, there is nothing of record to indicate that the skilled artisan would understand such language in the context of multiple dependent claims, but somehow would not reasonably understand the very same language in a singular dependent claim. Applicants respectfully request that the Examiner cite support for her belief that the use of an indefinite article in dependent claims is not allowed, or explain why the skilled artisan is not reasonably apprised of the scope of the invention by the claims as written.

"*insensitive*"

With respect to the term "insensitive" recited in claims 69-72 and 74, the Examiner contends that the term is a subjective term that allegedly lacks a comparative basis for defining its metes and bounds. Applicants respectfully disagree.

It is respectfully submitted that the term "insensitive" is a functional limitation that is clearly defined in the specification, *e.g.*, on page 8, lines 19-26 and page 11, lines 18-30. The

skilled artisan is fully informed that the an "insensitive" antibody, as referred to in the claims, refers to an antibody that, when used in an immunoassay, will provide an assay response value that is the same, at least within about a factor of 2, for each form of cardiac troponin I.

Those of ordinary skill in the art are well aware of immunoassay methods, and understand that antibodies can be used in such methods to perform a number of functions. For example, as described in the instant specification on page 24, line 30, through page 25, line 31, an insensitive antibody may be linked to a solid phase for use in competitive or sandwich-type immunoassays; alternatively, an insensitive antibody can be conjugated to a signal development element. The precise purpose to which the insensitive antibody is put is appropriately left to the discretion of the skilled artisan. Nevertheless, the skilled artisan is capable of determining whether the signal obtained from the immunoassay is within a factor of two, regardless of the form in which cardiac troponin I appears in the sample, thus meeting the functional limitation in the claims. Moreover, the instant specification provides examples of such a determination to further inform the skilled artisan of the meaning of the term "insensitive." *See, e.g.*, specification, page 62, Example 10

Additionally, it is well established that Applicants are free to be their own lexicongraphers, and can define in the claims what they regard as their invention essentially in whatever terms they choose. Applicants may use functional language, or any style of expression or format of claim which makes clear the boundaries of the subject matter for which protection is sought. MPEP 2173.01. Applicants respectfully submit that the term "insensitive" used in these claims is clearly defined in the specification, and is a functional limitation to the claim. As described in MPEP §2173.05(g), a functional limitation in a claim "is an attempt to define something by what it does, rather than by what it is." Such limitations "must be evaluated and considered, just like any other limitation of the claim." *Id.*

Because the skilled artisan is reasonably informed as to the meaning of the term "insensitive" as it is used in the instant claims, Applicants respectfully submit that the instant claims meet the definiteness standard of 35 U.S.C. § 112, second paragraph. Applicants, therefore, respectfully request that the Examiner withdraw the rejection.

"Assay response"

With respect to the phrase "assay response" used in claim 71, the Examiner contends that it is allegedly unclear what is encompassed by the phrase. Applicants respectfully submit that the phrase "assay response" refers to the detectable signal that is obtained from an immunoassay, which may be correlated to the presence or amount of an analyte of interest. The concept of immunoassays generally, and of responses from such assays in particular, have been well understood by the skilled artisan for decades. See, *e.g.*, Feldman and Rodbard, Chapter VII "Mathematical Theory of Radioimmunoassay," *Principles of Competitive Protein-Binding Assays*, J.B. Lippincott Company, 1971. Moreover, numerous exemplary immunoassays, and the responses obtained therefrom, are provided in the instant specification.

Because the skilled artisan is reasonably informed as to the meaning of the phrase "assay response" as it is used in the instant claims, Applicants respectfully submit that the instant claims meet the definiteness standard of 35 U.S.C. § 112, second paragraph. Applicants, therefore, respectfully request that the Examiner withdraw the rejection.

Art-Related Remarks

35 U.S.C. § 102

The Examiner has rejected claims 55-64 and 74-82 under 35 U.S.C. § 102(b) as allegedly being anticipated by Bodor *et al.*, (Clinical Chemistry, 1992). Applicants respectfully traverse this rejection.

To anticipate a claim, the reference must teach every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). *See also, In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143.

The instant claims relate to antibodies that specifically bind to the cardiac-specific troponin I in both free and complexed forms in an immunoassay. In particular, the instantly claimed antibodies are able to bind to free cardiac troponin I, as well as to cardiac troponin I in a binary complex with troponin C, and to cardiac troponin I in a ternary complex with troponin C and troponin T, thereby providing a signal from an immunoassay that is within at least a factor of two for equimolar amounts of each isoform of cardiac troponin I.

In contrast, the Bodor *et al.* publication discloses eight monoclonal antibodies, five of which bind cardiac troponin I, and three of which react with both cardiac and skeletal troponin I *See*, Bodor *et al.*, page 2212, column 1. The Boder *et al.* publication, however, does not disclose any antibody that binds to cardiac troponin I in a ternary complex with troponin C and troponin T, or any antibodies that are insensitive with respect to all the recited troponin I forms.

Furthermore, to the extent that the Examiner contends that the claimed functional result would be an inherent property of the Bodor *et al.* publication, Applicants respectfully note that the mere fact that such a characteristic may occur is not sufficient to establish inherency. *See, e.g.*, MPEP §2112. Applicants note that an antibody that is capable of binding to free troponin I, for example, may be blocked from binding when troponin I is present in a ternary complex; thus, the Boder *et al.* publication does not inherently disclose any antibodies that meet the limitations of the instant claims. Should the Examiner disagree, Applicants respectfully request that the Examiner provide extrinsic evidence making it clear that the missing descriptive matter from the claims is necessarily present in the devices disclosed in the Boder *et al.* publication.

Because the Bodor *et al.* publication does not teach or suggest each and every element of the instant claims, no *prima facie* case of anticipation has been provided. Therefore, Applicants respectfully request that the Examiner withdraw this rejection.

35 U.S.C. § 103

The Examiner has rejected claim 73 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Bodor *et al.* Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three criteria must be met: there must be some motivation or suggestion, either in the cited references or in knowledge available to the ordinarily skilled artisan, to modify or combine the references; there must be a reasonable expectation of success in combining the references; and the references must teach or suggest all of the claim limitations. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991) *See also,* MPEP §2143.

As discussed above, Bodor *et al.* publication fails to disclose any antibody that binds to cardiac troponin I in a ternary complex with troponin C and troponin T, or any antibodies that are insensitive with respect to all troponin I forms. The Examiner contends, however, that identifying and selecting such antibodies "can be achieved by routine optimization procedure." Paper No. 6, page 8. But, even if this is true, the mere fact that such an antibody could be made is not sufficient to establish a *prima facie* case of obviousness. *See, e.g.*, MPEP §2143.01. The Examiner has failed to provide any motivation for the skilled artisan to select, from amongst the universe of possible binding specificities, those antibodies that are insensitive with respect to all the troponin forms referred to in the instant claims. Therefore, no *prima facie* case of obviousness has been established. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. 103.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the address and telephone number listed below so that they may be resolved without the need for additional action and response thereto.

Respectfully submitted,

Date: November 15, 2001

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Novel Methods for the Assay of Troponin I and T and Complexes of Troponin I and T and Selection of Antibodies for Use in Immunoassays

Cross-Reference to Related Applications

This application is a continuation-in-part of U.S. Patent Application No. 08/633,248, filed April 18, 1996, issued as U.S. Patent No. 6,174,686, which is a continuation of U.S. Patent Application No. ~~serial~~ No. 08/423,582, filed 18 April 1995, ~~in the name of Kenneth P. Buechler and Paul H. McPherson~~, issued as U.S. Patent No. 5,795,725, each of which is incorporated by reference herein.

Technical Field

This invention relates to the assay of troponin I and troponin T and complexes of these proteins, and more specifically to the changes in conformation of these proteins in blood, serum and plasma and to the selection of antibodies to the various forms of these proteins and their use in immunoassays. In another aspect of the invention, compositions are taught for the stabilization and recovery of troponin I and T and their complexes in immunoassays.

Background Art

Myocardial infarction is one of the leading causes of death in the United States. Approximately 5 million individuals experiencing chest pain are evaluated every year in hospitals throughout the United States, however, less than 30%, of these individuals are subsequently found to have had a myocardial infarction. The accurate and rapid diagnosis of myocardial infarction is important both for the patient suffering a myocardial infarction and for the health care system which can minimize the costs incurred by rapidly identifying individuals who do need treatment.

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ABSTRACT OF THE DISCLOSURE

~~Assay systems and specialized antibodies for the detection and quantitation of troponin I and troponin T in body fluids as an indicator of myocardial infarction. Since troponin I and T exist in various conformations in the blood, the ratios of the monomeric troponin I an T and the binary and ternary complexes, as well as which form of troponin present in the blood, may be related to the metabolic state of the heart. Disclosed is a system to determine the presence of a troponin form or a group of troponin forms in a sample of whole blood, serum or plasma.~~

~~Disclosed is a stabilized composition of troponin; the stabilized composition can comprise a stabilized composition of troponin I, wherein the troponin I is oxidized, the troponin I can be unbound or the troponin I can be in a complex.~~

~~Disclosed is a method for improving the recovery of troponin I or T from a surface used in immunoassays~~

~~Also disclosed are antibodies which recognize, unbound troponin forms, the forms of troponin in binary complexes, the ternary complex of troponin I, T and C, and the conformations of troponin I having intramolecularly oxidized and reduced cysteines.~~

Antibodies and methods are described for the detection and quantitation of cardiac specific troponin I in samples. Cardiac-specific troponin isoforms exist in various forms in the blood, including free and complexed forms. By selecting antibodies that are insensitive and/or sensitive to these various forms, the present invention can provide immunoassays that more accurately reflect the clinical state of an individual. These described antibodies and methods can be used for providing indicators of myocardial infarction and other cardiac pathologies.

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